Highlights of the 24th Annual Meeting of the American Academy of Pain Medicine CME/CE

Complete author affiliations and disclosures are at the end of this activity.

Release Date: March 31, 2008; Valid for credit through March 31, 2009

Target Audience

This activity is intended for clinicians specializing in the field of pain management.

Goal

The goal of this activity is to provide an overview of several presentations given at the 24th annual meeting of the American Academy of Pain Medicine.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Examine the role of pain policy on opioid prescribing habits.
2. Discuss the impact of drug diversion in the United States.
3. Review the latest data on opioid use and hyperalgesia.

Credits Available

Physicians - maximum of 1.0 *AMA PRA Category 1 Credit(s)*™ for physicians;
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Contents of This CME/CE Activity

Laws and Regulations Affecting Opioid Prescribing

You've seen the headlines. "Pain Doctor Found Guilty of Drug Trafficking," and "Healer or Drug Dealer?" Add to these the overblown media coverage of a tragic consequence of nonmedical use of prescription medications, and it's enough to make anyone nervous about prescribing pain medications. Regulatory scrutiny of prescribing practices and criminal prosecution, real threats or no, can contribute to the already considerable problem of unrelieved pain.[1]

The relief of pain is a fundamental human right.[2] Yet some patients with acute pain, chronic nonmalignant, and cancer pain continue to suffer needlessly, despite the availability of effective treatments. Efforts to address unrelieved pain can be thwarted by simultaneous efforts to control drug abuse and addiction. This begs the question: can the legitimate relief of pain coexist with the war on drugs?

At the American Academy of Pain Medicine's 24th Annual Meeting in Orlando, Florida, Aaron M. Gilson, PhD, MSSW, of the PPSG at the University of Wisconsin at Madison, took the podium to address an issue of vital importance to the pain medicine community: laws and regulations that affect the management of pain.[3]

State pain policies address both the control of drugs and the standards of professional practice with regard to the treatment of pain. Although they do not carry the force of law, state pain policies can influence pain management and the availability of effective pain medications. Such policies authorize the medical use of drugs, define unprofessional conduct, prohibit unauthorized distribution of controlled substances, and restrict prescriptive practices. On the other hand, state policies can also recognize the value of controlled substances in a medical context, encourage pain management, and address barriers to effective pain management.

The Balanced Pain Policy

If pain is to be effectively managed, the principle of balance must govern medicine, controlled substances; and the protection of public health and safety. Opioid analgesics are necessary for relief of severe pain, such as that caused by cancer, but they do pose risks and must be prescribed with careful documentation. The legal designation of opioid analgesics as controlled substances does not diminish the medical usefulness of these drugs. Healthcare professionals can relieve pain in their patients without contributing to the abuse of opioid analgesics. Likewise, law enforcement and regulation can address drug diversion without interfering in medical practice and patient care.

The balanced pain policy recognizes that while controlled substances have a useful and legitimate medical purpose and are necessary to the health and welfare of the population, the illegal and improper use of controlled substances can also have substantial and detrimental effects on this same population. The prevention of drug abuse, an important public health goal, need not hinder proper patient care. A balanced pain policy does not authorize the use of medications outside an established system of control, but it values the prescribing of opioid analgesics by properly licensed healthcare professionals for legitimate medical purposes.[4]

Misunderstanding of Addiction

There is no denying that the use of opioid pain medication carries the stigma of drug abuse and addiction. It is a perception based on ignorance of the true nature of addiction and a belief that pharmacologic tolerance, physical dependence, and addiction are all the same. Although they can hinder the adequate treatment of pain, misunderstandings of this nature linger among practitioners, the general public, authors of professional textbooks, and those who write pain policy.[4]

Tolerance and physical dependence are normal consequences of sustained opioid use and are not synonymous with addiction. The AAPM, American Pain Society, and American Society of Addiction Medicine differentiate these concepts as follows[5]:

- Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestation. It is characterized by behaviors that include one or more of the following: impaired control over drug use, continued use despite harm, and craving.
- Physical dependence is a state of adaptation that is manifested by a drug class-specific syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.
- Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

Addiction, unlike physical dependence and pharmacologic tolerance, is not a predictable drug effect. Exposure to opioids is only one of the causative factors in the development of addiction. Patients treated with prolonged opioid therapy usually develop physical dependence and sometimes develop tolerance, but most do not develop an addiction.[3]

Examining Pain Policy

It is essential for practitioners to know the laws and policies under which they practice. In recent years, we have witnessed an increasing trend among states to implement policies regarding pain management. Currently, 47 states and the District of Columbia have pain policies. Alaska, Delaware, Illinois, and Indiana do not have pain policies at the state level.[3]

The goal of state pain policies is to enhance patients' chances of accessing appropriate pain management.[5] Pain policies should reassure practitioners that pain management is not only accepted, but is also expected as part of quality patient care.[4]

The PPSG developed a research methodology to systematically analyze public policy affecting pain management. The PPSG collected and analyzed state policies (laws, regulations, and guidelines) on prescribing controlled substances for pain management and compiled these data into a policy evaluation tool. Grounded in the unifying principle of balance between regulating controlled substances and prescribing them to relieve pain and suffering, the most recent version of the document, "Achieving Balance in Federal and State Pain Policy" was released in 2007.[6]

Criteria for Evaluating Pain Policy

The PPSG evaluation tool offers 16 criteria, based on the principle of balance, that can be used to appraise and revise state pain policy language. Half of these criteria are positive in tone, denoting language that can enhance pain management:

- Controlled substances are necessary for the public health;
- Pain management is general medical practice;
- Medical use of opioids is legitimate professional practice;
- Pain management is encouraged;
- Practitioners' concerns about regulatory scrutiny are addressed;
- Prescription amount is insufficient to determine legitimacy;
- Addiction is not confused with physical dependence or analgesic tolerance; and
- Other positive language.

In contrast, language that describes negative provisions can impede pain management:

- Opioids are a last resort;
- Opioids are outside legitimate professional practice;

- Addiction is confused with physical dependence or analgesic tolerance;
- Medical decisions are restricted (based on patient characteristics, mandated consultation, quantity of allowable prescription, or undue prescription limitations);
- Prescription validity is restricted;
- Additional prescribing requirements are imposed;
- Other restrictive language; and
- Ambiguous language.[5]

Restrictive, ambiguous language does not reflect current standards of professional practice and should be purged from pain policy. Examples of outdated beliefs that can still be found in some state pain policies include reserving opioids for a treatment of last resort, equating long-term use of opioids for pain with addiction, requiring "drug holidays" for patients with chronic pain, and imposing limitations on the quantity of pain medication that can be prescribed, regardless of patient need.[7]

Address Fear of Regulatory Scrutiny. Pain policies should contain explicit reassurances that physicians and other practitioners will not be scrutinized when they prescribe controlled substances for pain management. Currently, 39 state pain policies incorporate provisions that address these concerns. Three states also establish immunity from criminal prosecution. The remaining state policies are silent on the issue of practitioner scrutiny.[8]

Clarify Addiction and Physical Dependence. State policy that fails to distinguish between addiction and physical dependence does a disservice to patients and practitioners by focusing disproportionately on the abuse potential of opioids.[9] In their pain policies, 36 states clarify the difference between addiction and physical dependence, and 16 states continue to confuse these concepts. Contradicting regulations exist in states that use different definitions of addiction in different policies.[7] Persisting confusion is largely a consequence of adopting an outmoded 1969 federal definition of addiction.[3]

Restrictions on Prescribing. Eight state pain policies contain language that restricts the quantity of prescription medications that can be prescribed and dispensed at one time. These provisions usually stipulate either a maximum number of dosage units (100-120) or duration (30-day or 1 month's supply). A handful of states policies also restrict the length of time that a schedule 2 prescription is valid to less than 2 weeks. Eight states restrict prescribing for patients with pain and addictive disease. Seven states require opioids to be the "treatment of last resort."

State Pain Policy Report Cards

In 2000, the PPSG began evaluating state pain policies and assigning grade letter scores to each state based on the quality of its pain management policies. In "Achieving Balance in State Pain Policy: A Progress Report Card 2007," the PPSG compared pain policy grades from 2000, 2003, 2006, and 2007.[8] These findings allow evaluation of state pain policy over time, support goal-setting, and increase visibility of the need to improve pain policy.

The chief finding of the PPSG report was that state pain policies are becoming more balanced. Since 2006, of 23 states that made policy changes, 8 states made changes sufficient to improve their grades. Kansas and Wisconsin achieved an A, joining Michigan and Virginia as the states with the most balanced pain policies. By 2007, 86% of states received a grade above C and no state's grade has decreased since 2000. These improvements were credited to states adopting policies encouraging pain management, palliative care, or end-of-life care, and state legislatures repealing restrictive or ambiguous policy language.[8]

Many improved state policies resulted from the "Model Policy for the Use of Controlled Substances for the Treatment of Pain," generated by the Federation of State Medical Boards of the United States.[9] The model policy is offered as a template for the construction or revision of pain management policy.[10] The model policy communicates the messages that controlled substances are necessary for public health, and that pain management is part of quality medical practice for all patients with pain, acute or chronic, and especially for patients who experience pain as a result of terminal illness. The model policy emphasizes that prescribers should not fear regulatory sanctions and that the dosage or duration of prescriptions alone will not determine legitimacy of treatment.[9]

Beyond Policies

A lack of knowledge of medical standards, current research, and clinical guidelines for appropriate pain treatment contributes to the undertreatment of pain, as does a lack of understanding of state regulatory policies and practices. Writing a balanced pain policy is not enough to ensure pain management for those who need it.[3] To become part of established practice, a pain policy must be communicated and disseminated to those who will implement it and those who are affected by it. If the critical messages that state pain policy encourages pain management and healthcare professionals who treat pain should not fear unwarranted intrusion from

licensing agencies are heard by all, the undertreatment of pain should become a thing of the past.[3]

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Drug Diversion in the United States

Drug diversion, broadly defined, is when the legal supply chain of prescription analgesic drugs is broken, and drugs are transferred from a licit to an illicit channel of distribution or use. This definition, however, doesn't specify the who, what, when, where, how much, and for what purpose drug diversion occurs. These are questions that must be answered if we are to maintain the integrity of the opioid prescription drug supply to benefit patients with pain that does not respond to lesser means.

When opioid-related deaths receive intense media attention, people are quick to assign blame to prescribers, even though numerous routes of prescription drug acquisition are available. Media reports can exacerbate fears about medical use of prescription drugs among patients with pain and increase concerns about regulatory scrutiny among legitimate prescribers and dispensers.[1] Rarely do such reports focus on the true nature of prescription drug diversion.

Who Is to Blame?

A major obstacle to ending drug diversion, according to David Joranson, MSSW, Senior Science Director, PPSG, University of Wisconsin School of Medicine and Public Health in Madison, is the widespread belief that the full responsibility for the integrity of the drug supply chain rests with the prescriber.[2] Joranson argues that it is time to distribute fairly the responsibility for the problems of drug diversion and prescription drug abuse within a new paradigm. This paradigm takes a public health approach, rather than an exclusive law enforcement approach, to the complex problems of opioid abuse, addiction, and diversion.

Parallel to the increase in the use of opioid analgesics for pain management in recent years is a rise in the use of these drugs for nonmedical purposes. Opioid analgesic mortality has been attributed to more aggressive pain management.[3] The relationship between increased opioid prescribing and the misuse of opioids is not clear, however, and efforts to end diversion by restricting legitimate pain management are misguided. If we mistakenly believe that drug diversion and abuse stem only from inappropriate prescribing, our view of the medical treatment of pain will be "distorted through the lens of substance abuse."[4] Sources of drug diversion must be tackled head on, without impeding the legal availability of opioid analgesics, medical practice, or patient care.[5]

Mechanisms of Drug Diversion

Drug diversion occurs at every point in the drug supply chain. According to Joranson, a primary route of opioid diversion takes place at the wholesale level of manufacturing and distribution and includes the theft of medications in transit. The next layer of diversion occurs at the retail level, where the theft of drugs by employees and others takes place from hospitals and pharmacies. Nurses, the largest group of healthcare professionals pilfering opioid analgesics from hospital supplies, represent a group of impaired health professionals who need assistance to cease these actions.[6] Although legitimate Internet pharmacies exist, diversion also occurs through the use of stolen or forged prescriptions and the sale of controlled substances without prescriptions. At the patient level, inappropriate prescribing ("pill mills" and "script docs") and the seeking of prescription drugs under false pretenses ("doctor shopping") can be routes of drug acquisition for nonmedical purposes. Theft, sale, or improper disposal of legitimately prescribed medications also contributes to the pool of diverted drugs.

The demand for prescription drugs for illicit use is undeniably powerful.[7] People obtain and consume unprescribed drugs for many reasons. Although some divert drugs for monetary gain, abusers, addicts, and impaired healthcare professionals may take the illegally acquired drugs themselves. Other nonmedical uses of prescription drugs include taking for recreational reasons/getting high; taking compulsively for addiction; self-medicating for mood, sleep, or pain; or taking to alleviate withdrawal symptoms.

Scope of Drug Diversion

When controlled substances are lost or stolen, pharmacists, manufacturers, and distributors must report these occurrences to the US Drug Enforcement Administration (DEA). DEA data reveal that in the 4-year period from 2000 through 2003, nearly 28 million dosage units of all controlled substances were diverted by theft or loss from lawful channels, of which 24% were opioid analgesics.[4] Thefts, primarily from pharmacies, occurred in 12,894 separate incidents and involved hydrocodone, oxycodone, morphine, methadone, meperidine, hydromorphone, and fentanyl. Diversion of all drugs except morphine increased between 2000 and 2003. This is clear evidence that a considerable volume of drugs is being diverted through criminal actions from the drug distribution chain before being prescribed.

Approximately 6500 pharmacy thefts occur annually in the United States, or about 17 per day. Many of these are armed robberies or nighttime break-ins. These numbers indicate that pharmacy theft is nearly as common as the 7400 yearly, or 20 per day, bank robberies that take place in the United States.[1] We rarely read or hear about pharmacy theft, yet it suggests a viable avenue for stopping drug diversion.[1]

Conclusion

The health implications of drug diversion are too important to leave entirely to law enforcement. Efforts to prevent drug diversion must be evidence-based. The remedy for drug diversion will not be found in tightening prescription requirements for opioid analgesics because although prescribing is part of the problem, it is not the whole problem. Preventing drug diversion will require a long-term public health initiative, because an issue of even greater importance to public health is the inadequate treatment of patients with serious pain disorders.

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Opioid-Induced Pain Sensitivity

Try saying this to the patient who comes in to the office complaining of pain that is unrelieved by his or her current regimen of opioid analgesics: "We need to reduce your pain medicine." How well will most patients accept the explanation that their medication is actually increasing their pain?

Opioids are often the analgesics of choice for treating severe acute and chronic pain. But pain relief may not be the only effect of opioids. Exposure to opioids can result in 2 dissimilar processes: the development of opioid tolerance and the development of opioid-induced pain sensitivity, or hyperalgesia.[1] Sensitization and desensitization are both taking place.[2]

Opioid-induced pain sensitivity is a phenomenon that we are only beginning to understand, according to Jianren Mao, MD, PhD, of the Massachusetts General Hospital Center for Translational Pain Research.[3] Many studies have reported that opioid administration causes an unanticipated hyperalgesia (enhanced pain response to noxious stimuli) and allodynia (pain elicited by innocuous stimuli) in both animals and humans.[1]

Preclinical research suggests that abnormal pain sensitivity such as hyperalgesia or allodynia occurs in the absence of overt opioid withdrawal in animals that have been administered opioid drugs. Opioid-induced hyperalgesia can occur with both acute and chronic opioid administration.[3] A paradoxic opioid-induced pain sensitivity may contribute to apparent opioid tolerance in humans because the individual must increase the analgesic dose to maintain the same effect or the duration of action of the opioid will decrease.[4] Both continuous infusion and bolus injections of opioids shift the analgesic dose-response curve to the right so that progressively higher opioid doses are required for the same analgesic effect.

A reduction of the baseline nociceptive threshold following repeated opioid administration is the presumed mechanism of increased pain sensitivity in animals. Intrathecal morphine sulfate, administered twice daily, progressively lowers the baseline nociceptive threshold in rats, as does the administration of subcutaneous fentanyl or heroin boluses. Similar findings occur with continuous opioid infusion.

The relationship between abnormal pain sensitivity and opioid withdrawal is known. Dr. Mao proposes that the lower baseline nociceptive threshold observed in animals is a miniwithdrawal of sorts and precedes the more recognizable withdrawal signs such as diarrhea, wet-dog shake, and jumping. Signs of withdrawal in humans include nausea, ataxia, vomiting, diarrhea, and altered sense of smell.

Cellular Mechanisms of Opioid-Induced Pain Sensitivity

Opioid-induced pain sensitivity is an active process within the central nervous system, mediated through distinct neural mechanisms, including the endogenous dynorphin system, the glutamatergic system, and descending facilitation. These neural mechanisms are similar to those involved in neuropathic pain and involve the NMDA receptor and associated cascades.[5]

Peripheral nerve injury and repeated opioid administration similarly activate the central glutamatergic system. Hyperalgesia from tissue injury and inflammation is caused by prolonged excitation of spinal cord amino acid receptors and second messenger systems. Phosphorylation and sensitization of NMDA receptors follow. Hyperalgesia caused by fentanyl or heroin can be blocked by NMDA receptor antagonists.

Pain sensitization is believed to be mediated by tonic nociceptive afferent input from tissue injury or inflammation, causing:

- Toxic effect of opioid metabolites (morphine-3-glucuronide (M3G) or hydromorphone-3-glucronide (H3G);
- Central sensitization as a result of opioid-related activation of NMDA receptors in the central nervous system;
- Increase in spinal dynorphin activity;
- Enhanced descending facilitation from the rostral ventromedial medulla; and
- Activation of intracellular protein kinase C.

There is not yet any direct evidence for opioid-induced heightened pain sensitivity in humans. Self-reports of pain scores cannot distinguish pharmacologic tolerance from increased pain sensitivity. Similarly, observations documenting reduced postoperative analgesic efficacy following intraoperative opioid infusion suggest opioid tolerance but do not make a distinction between pharmacologic tolerance and opioid-induced pain sensitivity or both. In support of the theory of increased pain sensitivity is the finding

that patients treated intraoperatively with opioids reported more postoperative pain than matched non-opioid controls.[6,7]

Pain sensitivity also differs between subjects with opioid addiction and normal subjects, with increased pain sensitivity to an experimental pain stimulus in those with opioid addiction. Moreover, pain sensitivity is altered in patients undergoing methadone maintenance. In these individuals, pain sensitivity is increased beyond that of former opioid addicts who are not receiving methadone.[8]

In patients with cancer or other types of chronic pain, it is difficult to separate increased pain sensitivity from increases in disease-related pain. Although anecdotal reports suggest that opioid-induced pain sensitivity does occur in patients with cancer pain, controlled studies of pain sensitivity in these patients are lacking. In a small prospective study of patients with nonmalignant chronic pain, patients were evaluated for opioid tolerance and opioid-induced hyperalgesia. Quantitative sensory testing was performed in 6 patients with chronic low back pain before and 1 month after starting morphine treatment. Pain sensitivity to experimental cold and heat pain was measured during administration of a short-acting mu-opioid agonist. Hyperalgesia and tolerance developed with cold pain but not with heat pain.[9]

Clinical Implications

The patient without apparent disease progression who reports diminishing analgesic efficacy during opioid therapy presents a dilemma. Traditionally, we have assumed that an increased opioid requirement for the same analgesic effect was primarily a sign of pharmacologic tolerance, or possibly a worsening disease state. The usual approach to this situation is to increase the dose of opioid to overcome tolerance or more effectively treat pain. The paradox of opioid-induced pain sensitivity compels us to rethink this approach. Rather than escalating opioid dosages, opioid tolerance caused by increased pain sensitivity is managed by *lowering* opioid dosages.

How does the clinician determine whether reported pain is preexisting or opioid induced? Dr. Mao suggests 4 tests that can be used to differentiate between the two:

1. Pain intensity is increased above the level of preexisting pain in the absence of apparent disease progression;
2. Opioid-induced pain is diffuse, less defined in quality, and beyond the distribution of the preexisting pain state;
3. Quantitative sensory testing (eg, tolerance to cold and heat pain) may reveal changes in pain threshold, tolerability, and distribution patterns; and
4. Undertreatment of preexisting pain or development of pharmacologic tolerance may be overcome by a trial of opioid dose escalation. In contrast, opioid-induced pain could be worsened by an increase in opioid dose. Opioid-induced hyperalgesia will improve after supervised opioid tapering.[2]

Clinical evidence suggests that the degree of opioid-induced hyperalgesia varies with different opioids. Morphine, for instance, is more likely to produce hyperalgesia than methadone. Duration of treatment may also influence the development of opioid-induced hyperalgesia, although this phenomenon has been noted in patients receiving short-term opioid therapy. It is not yet known whether switching opioids interrupts this process.

Summary

Pharmacologic tolerance or worsening disease state are not the sole explanations for a decrease in analgesic efficacy. When presented with the patient who reports increasing pain or failure of current therapy to provide adequate analgesia, the clinician should consider the possibility of opioid-induced hyperalgesia. Under some circumstances, a trial of opioid tapering might achieve pain reduction.

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The Dark Side of Drug Addiction

Drug addiction is a chronic relapsing disorder. Neurobiological changes are the basis for compulsive drug-taking, accompanied by loss of control over drug intake and the emergence of a negative emotional state when access to the drug is blocked.[1,2] Clinically, a distinction is made between the escalated drug use of addiction and the occasional but limited taking of drugs with the potential for abuse and dependence.[2]

As addiction develops, neuroplastic brain reward systems are transformed.[3] This is the "dark side" of drug addiction: the decline in normal reward-related neural mechanisms and persistent recruitment of the brain's antireward systems that accompany drug use.[3] Progressive worsening of the brain reward system perpetuates compulsive use of the drug.[4]

George F. Koob, PhD, of the Scripps Research Institute in La Jolla, California, studies the behavior of rodents in an effort to understand the neuropharmacologic and neuroadaptive mechanisms that enable the crossover from occasional, controlled drug user to the behaviors of an addict.[5] Knowledge of these neurochemical systems may elucidate vulnerability to addiction and suggest pharmacotherapies for drug addiction.[3]

Cycle of Addiction

Drug addiction has elements of both an impulse control disorder and a compulsive disorder that are mediated by separate but overlapping neural circuits. The individual with an impulse control disorder experiences an increasing sense of tension or arousal before committing the impulsive act such as drug-taking; pleasure, gratification or relief during the act; and in some cases, regret, self-reproach or guilt following the act.[4] The individual with a compulsive disorder feels anxiety and stress before the compulsive, repetitive act, and relief from stress by performing the act. In the progression from an impulsive disorder to a compulsive disorder, the motivation for the behavior shifts from positive reinforcement to negative reinforcement, when removal of the aversive state increases the probability of the behavior.[3] Drug addiction follows this pattern in a collapsed cycle of addiction involving 3 stages:

- Binge/intoxication;
- Withdrawal/negative affect; and
- Preoccupation/anticipation (craving).

Addiction involves a long-term persistent plasticity of the neural circuits that control 2 different reward systems: declining function of brain reward systems driven by natural rewards and stimulation of antireward systems that bring on aversive states.[3]

Brain Reward System

Studies of the acute reinforcing effects of drugs of abuse in the binge/intoxication stage have identified the neurobiological substrates involved in the reward response. Drugs with the potential for abuse and dependence, such as the opioid analgesics, initially produce positive reinforcing effects from actions at the ventral tegmental area in the midbrain and the nucleus accumbens and amygdala of the basal forebrain.[2] Activation of the mesocorticolimbic dopamine pathway is the primary route of positive reinforcement in addiction for psychostimulant drugs, but the opioid peptides (endorphins), serotonin, and gamma-aminobutyric acid (GABA) have key roles for nonpsychostimulant drugs. These so-called "reward neurotransmitters" induce hedonic effects of euphoria and a feeling of well-being.

Brain Antireward System

Withdrawal from a drug of abuse induces symptoms of negative affect such as dysphoria, depression, irritability, and anxiety.

Dysregulation of brain reward systems involves some of the same neurochemical pathways implicated in the drug's acute reinforcing effects, but in this case, they represent an opponent process.[4,6] During acute abstinence, increases in brain reward thresholds (a higher set point for drug reward) are a consequence of altered reward neurotransmitters. This in turn may contribute to the negative motivational state of withdrawal and vulnerability to relapse.[2] Neurochemical changes during opioid withdrawal include decreases in dopaminergic and serotonergic transmission and increased sensitivity of opioid receptor transduction mechanisms. Escalating doses of opioids, like those seen in the human pattern of morphine or heroin use, are associated with profound alterations in the function of mu-opioid receptors.[1] A decrease in baseline reward mechanisms leads to an increase in drug intake to compensate for the shift in reward baseline.[7]

For the addict, the situation deteriorates.[8] Stress response systems of the body contribute to the negative emotional state associated with abstinence and can exacerbate drug taking throughout the addiction cycle. In response to taking the drug, the neuroendocrine system kicks in to attempt to restore the brain to normal function.[2] Chronic drug use adversely affects the hypothalamic-pituitary-adrenal axis, disrupting regulation of hypothalamic corticotropin releasing factor (CRF). Particularly important is activation of CRF in the extrahypothalamic brain stress system of the extended amygdala. The extended amygdala is a structure comprised of the bed nucleus of the stria terminalis, the central nucleus of the amygdala, and a transition zone in the medial subregion of the nucleus accumbens and a major projection to the lateral hypothalamus.[8] CRF controls hormonal, sympathetic, and behavioral responses to stress. During acute withdrawal of the drug, production of adrenocorticotropic hormone, corticosterone, amygdala CRF, norepinephrine, dynorphin, and inhibition of neuropeptide Y induce brain arousal, stress-like responses, and a dysphoric, aversive state. The activation and recruitment of brain and hormonal stress responses contribute to a deviation in brain reward set point.[7] These are the sources of negative reinforcement that lead to compulsive drug-seeking behavior and addiction.

Craving and Relapse

The preoccupation/anticipation stage of the addiction cycle is mediated via afferent projections to the extended amygdala and nucleus accumbens. There are different stimuli for craving a drug of abuse, leading to relapse. It can be drug-induced, cue-induced, or stress-induced.[3]

Chronic relapse is a significant problem in drug addiction, with about half of all addicts relapsing into drug taking.[8] Addicts can return to compulsive drug taking long after acute withdrawal exhibiting behavior that corresponds to the preoccupation/anticipation stage of addiction.[4] Drug-related cues and stressors are a powerful inducement to return to drug use.[8] Areas of the brain associated with drug and cue-induced reinstatement are the prefrontal cortex (orbitofrontal, medical prefrontal, prelimbic/cingulate), and the basolateral amygdala. The neurotransmitters involved in relapse are dopamine, opioid peptides, glutamate, and GABA. Relapse can also be precipitated by stress and the release of CRF, glucocorticoids and norepinephrine. Many different stressors can provoke drug craving and drug-seeking behavior.[8]

Animal Studies

It has been possible to study the effects of both short- and long-term exposure to drugs of abuse in a rodent extended-access model. This animal model has been used to study the transition from drug use to addiction, including such behaviors as escalating drug intake driven by dependence, self-administering drug despite adverse consequences, and a narrowing of the behavioral repertoire for drug seeking.[5,7] Extended access to drugs of abuse produces dramatic increases in drug intake and dependence over time that mirror human behavior. Extended access also produces anxiety-like responses mediated by an increase in extracellular CRF secreted by the central nucleus of the amygdala during withdrawal, effects that are reversed by CRF receptor antagonists. Giving a CRF receptor antagonist blocks excessive drug taking, providing promise for a possible treatment for addiction.[6]

Evidence from animal research also supports the similarities between stress and drugs of abuse in their effects on neurochemistry, electrophysiology, and morphology of neurons in the reward pathway. Exposing a rodent to an acute stressor increases the release of CRF and corticosterone in the hypothalamic pituitary adrenal axis, which in turn activates CRF in the amygdala. Molecular studies support the concept that stress and addictive drugs act through common molecular mechanisms within similar brain circuits to perpetuate the addiction cycle.[8] The long-lasting nature of addiction suggests that changes in gene expression might be required for the development and persistence of this disease.[8]

Summary

Rewards are pleasurable, but addictions hurt. The neurobiological underpinnings of reward and addiction involve different but overlapping neuroanatomic circuits.

Addiction is not a single incident, but rather occurs by a series of events initiated by the acute rewarding effects of drugs followed by a transition into chronic drug use.[8] Drug addiction is associated with a long-term persistent decrease in the function of normal motivational systems driven by 2 sources: (1) decreased function of brain reward systems (mediating natural rewards) and (2) increased antireward systems recruited in an opponent process to excessive activation of the brain reward system.

The deficit state for normal reward that is produced by excessive drug taking, rather than a hyperactive or sensitized reward state for drugs per se, is the motivation to seek drugs. Excessive drug taking results in not only the short-term amelioration of the reward deficit but also in suppression of the antireward system.[5]

Acute withdrawal of all major drugs of abuse increases brain reward thresholds, anxiety-like responses, and CRF in the amygdala that are of motivational significance. The amygdala has powerful emotional machinery, and brain stress responses recruit its dark side. Worsening of the underlying neurochemical dysregulations (decreased dopamine and opioid peptide function, increased CRF activity) lead to a chronic deviation of reward set point that is fueled not only by dysregulation of reward circuits but also by recruitment of brain and hormonal stress responses.[5] Brain arousal stress systems in the extended amygdala may be important not only for the negative emotional states that drive dependence on drugs of abuse but also may overlap with the negative emotional components of chronic pain syndromes.

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